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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
WEHBE, ANNE MARIE SABRINA	
ART UNIT	PAPER NUMBER
1633	

NOTIFICATION DATE	DELIVERY MODE
07/09/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentadministrator@clarkelbing.com

Office Action Summary	Application No.	Applicant(s)	
	10/562,408	YOU ET AL.	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 April 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/14/06,7/16/07,9/18/07,1/7/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response to the election of species requirement received on 4/20/09 has been entered. Applicant's election of the species "Sendai virus" without traverse is acknowledged. Claims 1-14 are currently pending and under examination based on the elected species of "Sendai virus", there being no allowable generic claim. An action on the merits follows.

Applicant's amendment to the specification to delete duplicate sentences has been entered.

The Information Disclosure Statements (IDS) filed on 8/14/06, 7/16/07, 9/18/07, and 1/7/08, have been considered and initialed and signed copies of the 1449s are attached to this action. Note that consideration of documents not published in English have only been considered based the provided English language abstract or translation.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 6-9, and 13-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 01/32898 (2001), hereafter referred to as Yonemitsu et al., in view of U.S. Patent No. 5,250,846 (1993), hereafter referred to as Collins et al. Please note that as the WO 01/32898 reference was published more than 1 year prior to the effective filing date and therefore qualifies as prior art under 102(b) that the provision of 103(c) cannot be used to overcome this rejection.

Yonemitsu et al. teaches recombinant Sendai virus vectors comprising a heterologous sequence encoding CFTR (Yonemitsu et al., entire document, particularly page 22, claim 5). Yonemitsu et al. teaches the minus strand RNA form of the recombinant Sendai virus vector and the DNA form of the vector (the sense strand) (Yonemitsu et al., page 8). Yonemitsu et al. further teaches that the CFTR sequence can be a modified CFTR sequence or a sequence encoding a functionally equivalent derivative of CFTR (Yonemitsu et al., pages 6 and 22, especially claim 5). Yonemitsu et al. further teaches methods of producing a recombinant Sendai virus comprising obtaining Sendai virus cDNA, inserting into the Sendai virus cDNA the foreign gene cDNA, and reconstituting the minus strand Sendai virus (Yonemitsu et al., pages 7-9).

Although Yonemitsu et al. teaches recombinant Sendai virus comprising a modified CFTR sequence, Yonemitsu et al. does not specifically teach to alter sequence in the CFTR sequence which is the same as a part of the Sendai virus E sequence. However, at the time of filing, Collins et al. teaches the introduction of silent mutations into the cDNA sequence of full length CFTR in order to stabilize vectors comprising the full length cDNA in bacteria (Collins et al., columns 7-8 and 11). In particular, Collins et al. teaches to mutate the A at position 933 in the CFTR sequence comprising GAAAA to a G to read GAGAA (Collins et al., columns 7-8 and 11). Please note that GAAAA is a sequence present in the Sendai virus E sequence such that the teachings of Collins to alter the sequence GAAAA to GAGAA inherently encompasses the alteration of a part of an antigenome E sequence present in CFTR. Therefore, in view of the teachings of Yonemitsu et al. to insert modified CFTR sequences which are functionally equivalent to the wild type sequence into Sendai virus, and the motivation to make silent mutations in the CFTR sequence, and particularly the mutation GAAAA to GAGAA, in order to stabilize the CFTR cDNA sequence during amplification in bacteria as taught by Collins et al., it would have been *prima facie* to the skilled artisan at the time of filing to insert the modified CFTR taught by Collins et al. into Sendai virus cDNA and then to reconstitute the minus strand Sendai virus comprising the modified CFTR antisense sequence. Further, based on the detailed guidance provided by Collins et al. for modifying the CFTR sequence, and the detailed guidance provided by Yonemitsu et al. for making recombinant Sendai virus comprising CFTR sequence, the skilled artisan would have had a reasonable expectation of success in making a recombinant cDNA or minus strand RNA Sendai virus comprising a modified CFTR sequence in which the sequence GAAAA has been altered to GAGAA.

Please note that while Collins et al. does not recognize that GAAAA is a sequence present in the Sendai virus E sequence, there is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference. *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003). Further, with respect to the intended use of the alteration to lower mutation frequency and to lower the identity with the Sendai virus E sequence, a preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure or composition, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. *In re Hirao* , 535 F.2d 67, 190 USPQ 15 (CCPA 1976); *Kropa v. Robie* , 88 USPQ 478, 481 (CCPA 1951).

Claims 1, 6-9, and 13-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 01/32898 (2001), hereafter referred to as Yonemitsu et al., in view of U.S. Patent No. 6,468,793 (2002), hereafter referred to as Teem. Please note that as the WO 01/32898 reference was published more than 1 year prior to the effective filing date and therefore qualifies as prior art under 102(b) that the provisions of 103(c) cannot be used to overcome this rejection.

Yonemitsu et al. teaches recombinant Sendai virus vectors comprising a heterologous sequence encoding CFTR (Yonemitsu et al., entire document, particularly page 22, claim 5). Yonemitsu et al. teaches the minus strand RNA form of the recombinant Sendai virus vector and the DNA form of the vector (the sense strand) (Yonemitsu et al., page 8). Yonemitsu et al. further teaches that the CFTR sequence can be a modified CFTR sequence or a sequence

encoding a functionally equivalent derivative of CFTR (Yonemitsu et al., pages 6 and 22, especially claim 5). Yonemitsu et al. further teaches methods of producing a recombinant Sendai virus comprising obtaining Sendai virus cDNA, inserting into the Sendai virus cDNA the foreign gene cDNA, and reconstituting the minus strand Sendai virus (Yonemitsu et al., pages 7-9).

Although Yonemitsu et al. teaches recombinant Sendai virus comprising a modified CFTR sequence, Yonemitsu et al. does not specifically teach to alter sequence in the CFTR sequence which is the same as a part of the Sendai virus E sequence. However, at the time of filing, Teem teaches modified CFTR sequences in which specific amino acid modifications result in CFTR proteins with higher CFTR channel activity that the wild type protein (Teem, columns 3-4 and 125-126). Teem specifically teaches mutation of the sequence encoding the amino acid at position 933 of CFTR from an arganine to lysine (Teem, columns 3-4 and 125-126). The nucleotide sequence at position 933 for arganine is AGA, which is a sequence present in the Sendai virus antigenome E sequence. Thus, alteration of the AGA sequence inherently encompasses alteration of a part of a Sendai virus antigenome E sequence. Therefore, in view of the teachings of Yonemitsu et al. to insert modified CFTR sequences which are functionally equivalent to the wild type sequence into Sendai virus, and the motivation to alter the CFTR sequence to increase activity, and particularly to mutate the arganine AGA codon to lysine as taught by Teem, it would have been *prima facie* to the skilled artisan at the time of filing to insert the modified CFTR taught by Teem into Sendai virus cDNA and then to reconstitute the minus strand Sendai virus comprising the modified CFTR antisense sequence. Further, based on the detailed guidance provided by Teem for modifying the CFTR sequence, and the detailed

guidance provided by Yonemitsu et al. for making recombinant Sendai virus comprising CFTR sequence, the skilled artisan would have had a reasonable expectation of success in making a recombinant cDNA or minus strand RNA Sendai virus comprising a modified CFTR sequence in which the sequence AGA has been altered.

Please note that while Teem does not recognize that GAAAA is a sequence present in the Sendai virus E sequence, there is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference. *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003). Further, with respect to the intended use of the alteration to lower mutation frequency and to lower the identity with the Sendai virus E sequence, a preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure or composition, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. *In re Hirao* , 535 F.2d 67, 190 USPQ 15 (CCPA 1976); *Kropa v. Robie* , 88 USPQ 478, 481 (CCPA 1951).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a recombinant Sendai virus comprising a nucleotide sequence whose

sense strand encodes human CFTR, where the human CFTR has been altered at the 5'-$AGA_{5-6}C$-3' sequence to lower the sequence identify with the E sequence of the Sendai virus, and wherein the alteration does not affect the amino acid sequence of the encoded human CFTR, and for methods of producing said recombinant Sendai virus comprising 1) altering one or more 5'-$AGA_{5-6}C$-3' sequences present in the human CFTR sequence to a different sequence(s) in order to lower the sequence identity to the Sendai virus E sequence and reduce the mutation frequency of the CFTR sequence, wherein the alteration does not affect the amino acid sequence of the encoded human CFTR, 2) preparing a DNA encoding the genome of the Sendai virus into which the altered CFTR sequence has been inserted, and 3) reconstituting the minus-strand RNA Sendai virus by transcribing the DNA, does not reasonably provide enablement for methods of making a recombinant Sendai virus or the Sendai virus itself as claimed where the virus comprises any foreign gene with any alteration of a sequence in common with the E sequence of the Sendai virus. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The specification generally discloses that the mutation frequency of a gene can be lowered by altering a sequence within the gene which is identical to part of the Sendai virus antigenome E sequence. The specification further discloses that the purpose for producing Sendai vector comprises foreign genes with lower mutability is to provide improved vectors for gene therapy, and specifically gene therapy for cystic fibrosis. Particular E sequences disclosed in the specification include 5'-$AGA_{5-6}C$-3' or 5'-$AGA_{5-6}CTT$-3'. However, of the enormous number of genes known in the art, the specification only identifies the human CFTR gene

sequence as comprising 5'-AGA$_{5-6}$C-3'. The specification also discloses that the human CFTR gene sequence when present in a Sendai virus genome produces a mutated CFTR gene with high frequency, and that mutation of the 5'-AGA$_{5-6}$C-3' sequence present in two regions of the CFTR gene reduced the mutation frequency of the CFTR gene in Sendai virus. The specification does not identify any other genes that are hypermutable when present in Sendai virus, or disclose that these genes comprise the 5'-AGA$_{5-6}$C-3' sequence or any other sequence present in an antigenome E sequence, or that alteration of the sequence reduces mutation frequency. In addition, while the specification discloses the alteration of the CFTR sequence to introduce silent mutations that do not alter the amino acid sequence of CFTR, the claims encompass any type of alteration in the 5'-AGA$_{5-6}$C-3' sequence or any other sequence in the CFTR gene which is the same as a part of an antigenome E sequence. The claims therefore encompass deletions and missense mutations which could inactivate the CFTR gene or result in a truncated protein with unknown activity. Such altered CFTR would have no predictable use in gene therapy of cystic fibrosis or any other disclosed application of the virus. Further in regards to decreasing mutation frequency in genes identified as being hypermutable in Sendai virus, the claims encompass an antigenome E sequence of any length that is present in the gene, such that the claims encompass a part of the E sequence which is only 2 nucleotides in length. The specification however demonstrates in the working examples the alteration of each incidence of a specific E sequence of at least 6 nucleotides, 5'-AGA$_{5-6}$C-3', and does not provide any specific guidance for any 2 or 3 or 4 nucleotides, etc., whose alteration would positively affect the mutation rate of CFTR or any other hypermutable gene sequence present in Sendai virus. It is also noted that the prior art at the time of filing is silent as to genes other than CFTR that are hypermutable in Sendai virus, and

is further silent as to specific parts of any length of a Sendai virus E sequence which when present in a gene cause hypermutability in Sendai virus other than 5'-AGA$_{5-6}$C-3'. Thus, the skilled artisan at the time of filing would not have been able to predict *a priori* which genes sequences might be hypermutable when present in Sendai virus, or whether the presence of a sequence with only 2, 3, or 4 nucleotides in common with a Sendai virus E sequence would cause hypermutability in Sendai virus, or whether alteration of a nucleotide within a sequence of 2, 3, or 4 nucleotides would be sufficient to reduce any mutability of the gene sequence when inserted in Sendai virus.

Thus, the specification, while providing sufficient guidance for alteration of a CFTR gene sequence 5'-AGA$_{5-6}$C-3' through the introduction of silent mutations in order to reduce its mutability in Sendai virus, the specification does not provide adequate guidance for genes other than CFTR which are hypermutable in Sendai virus, or for sequences of any length including sequences of 2, 3, or 4 nucleotides in length in the gene which are the same as sequence present in the Sendai virus E sequence which can be altered in any fashion to reduce mutability of the gene in Sendai virus. Therefore, based on the lack of guidance in the specification and prior art for the scope of the above identified elements of the instant claimed invention, the limitation of the working examples to alteration of the human CFTR gene at both incidences of the sequence 5'-AGA$_{5-6}$C-3' where the alteration does not affect the functionality of the encoded CFTR protein, and the breadth of the claims, it would have required undue experimentation to practice the full scope of the invention as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 9 and 13-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 9 recites a method for producing a minus-strand RNA virus carrying a gene which is altered to lower mutation frequency, where the gene before alteration comprises in its sense strand an antigenome E sequence of the minus-strand RNA virus, and wherein the gene before alteration comprises in its sense strand an antigenome E sequence of the minus-strand RNA virus comprising " (a) altering the part of the E sequence in the sense strand sequence to a different sequence". Step (a) is confusing as it is unclear whether the E sequence to be altered is present in the gene sequence or in the sense strand of the minus-strand RNA virus. It is suggested that applicant amend step (a) to recite " altering the part of the E sequence in the sense strand sequence of the gene to a different sequence", in order to overcome this rejection.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. If the examiner is not available, the examiner's supervisor, Joseph Woitach, can be reached at (571) 272-0739. For all official communications, the technology center fax number is (571) 273-8300. Please note that all official communications and responses sent by fax must be directed to the technology center

fax number. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737. For any inquiry of a general nature, please call (571) 272-0547.

The applicant can also consult the USPTO's Patent Application Information Retrieval system (PAIR) on the internet for patent application status and history information, and for electronic images of applications. For questions or problems related to PAIR, please call the USPTO Patent Electronic Business Center (Patent EBC) toll free at 1-866-217-9197. Representatives are available daily from 6am to midnight (EST). When calling please have your application serial number or patent number available. For all other customer support, please call the USPTO call center (UCC) at 1-800-786-9199.

Dr. A.M.S. Wehbé

/Anne Marie S. Wehbé/
Primary Examiner, A.U. 1633